European Journal of Physical Education and Sport Science
ISSN: 2501 - 1235
ISSN-L: 2501 - 1235
Available on-line at: www.oapub.org/edu

doi: 10.5281/zenodo.375659 Volume 3 | Issue 2 | 2017

CAN THE IRREGULAR ACETYLSALICYLIC ACID (ASA) THERAPY COMBINED WITH INTERVAL TRAINING EXERCISE PROGRAM INCREASE THE CLAUDICATION DISTANCE IN DIABETIC AND NON-DIABETIC PATIENTS WITH FEMORO-POPLITEAL STENOSIS AGE OVER 55

Sid Solaković[1], Mensur Vrcić[2], Ratko Pavlović[3i], Rubina Alagaić-Alimanović[4]

[1]Clinic for Vascular Surgery, Clinical Center of University of Sarajevo, Bosnia and Herzegovina

[2]Faculty of Sport and Physical Education, University of Sarajevo, Bosnia and Herzegovina

[3]Faculty of Physical Education and Sport, University of East Sarajevo, East Sarajevo, Bosnia and Herzegovina

[4]Clinic of Nuclear Medicine and Endocrinology, Clinical Center University of Sarajevo, Bosnia and Herzegovina

Abstract:

The aim of the study was to estimate the increasing capability of claudications distance in Fontaine's stage IIa of peripheral artery disease by influence of irregular acetylsalicylic acid (ASA) therapy and life style modification, combined with regular physical activity in diabetic and non-diabetic patients age over 55, in order to establish if there were any improvements in claudication distance in the both groups of patients. **Method:** This study was conducted from beginning of January, 2014 till end of January, 2015 at the Clinic of Vascular Surgery, Clinical Center University of Sarajevo and included 60 patients age over 55 (30 patients who have diabetes mellitus and impellers group consisting of 30 patients who were clinically confirmed not to have diabetes mellitus), male and female, in stadium IIa of peripheral artery disease, with manifestation of mild claudication symptoms. For the testing of statistical significance of differences between the exanimated groups non-parameter and parameter tests were used. The difference at a level of $p<0,05$ was statistically significant. **Results:** In all the

[i] Correspondence: email pavlovicratko@yahoo.com

tested patients, we investigated increasing of claudications distance in diabetic and non-diabetic patients age over 55 years after one year study. Analysis shows the statistically significant influence of antiplatelet therapy (Acetylsalicylic acid) (ASA), combined with physical activity and life style modification on claudications distance over 500 meters in 25 patients without diabetes mellitus in (83% p<0,05), compared to 12 patents with diabetes mellitus (40% p<0,05). Sixteen of non-diabetic patients (53%) were on antiplatelet therapy over 4 years, on permanent treatment, compared to 4 diabetic patients or (3%) (p<0,05). **Conclusion:** These clinical combined factors appeared to us as being the main strategy of the therapeutic effect on enhancement of claudication distance (Fontaine's stage II) of peripheral artery disease in patients with diabetes mellitus, as well as patients without it.

Keywords: peripheral artery disease, claudication distance, diabetes mellitus, physical activity, life style modification

1. Introduction

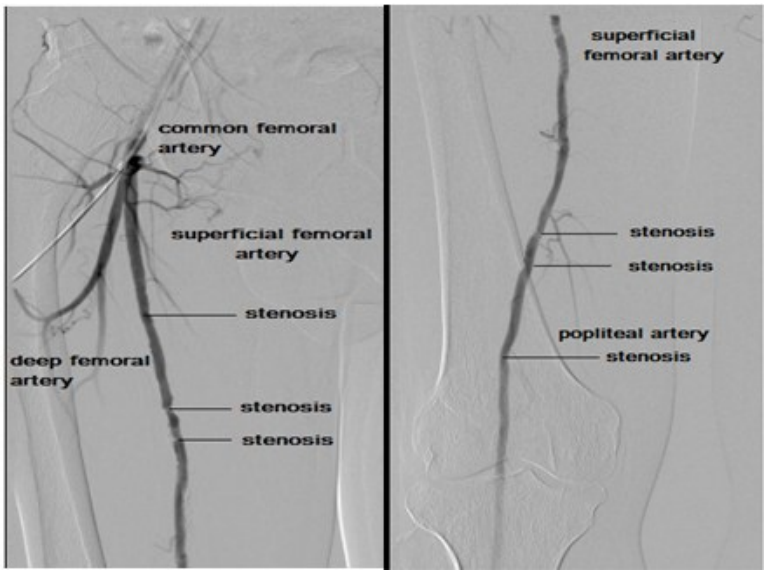
Peripheral artery disease (PAD) is a progressive disease occurring as a result of plaque accumulation progress (claudication based on atherosclerosis pathologic process, mostly on low extremities) in the arterial system that carries insufficient oxygenated blood to the extremities as well as vital organs and it is not to be underestimate. Peripheral artery disease (PAD) may cause barrier or blockage of vessels in the legs and other parts of the body distant from the heart; pain occurs as the result of a reduction in the blood flow to the muscles of the legs (Abbott, Brand, & Kannel, 1990; Creager, Luscher, & Cosentino, 2003; Thomas, Lüscher, Mark, & Creager, 2003). The diagnosis of PAD is difficult because most patients remain asymptomatic for many years. The symptoms do not appear until there is at least 50% or more reduction and obstruction of healthy lumen of Superficial Femoral Artery and Popliteal Artery narrowing stenosis witch causing the claudication (Izquierdo-Porrera, Gardner, Bradham, et al. 2005; Steg, Bhatt, Wilson, D'Agostino, et al. 2007). In Fontaine's stage IIa of peripheral artery disease the claudication symptomatology occurs in form of moderate and mild pain symptoms, caused by a distance greater than 200 meters. Certain conditions or habits may rise risk of peripheral artery disease (Thomas, Palumbo, Melton, et al. 2003; Belch, MacCuish, Campbell, et al. 2008). These conditions are known as risk factors. Before age 55, women have a lower cardiovascular risk than men. Estrogen provides women with certain protection against cardiovascular disease before menopause. After age 55,

however, the risk of cardiovascular disease increases in both, women and men. Peripheral artery disease has been viewed as a disease of the lower extremities typified by claudication symptoms (Criqui, Denenberg, et al. 1998; AACPR, 2004; Golomb, Dang, & Criqui, 2006; Berger, Roncaglioni, Avanzini, et al. 2006). Patient with diabetes mellitus has a two- to four times shorter life expectancy, referring to complications caused by progression of cardiovascular disease. Diabetes and pre-diabetic stage highly increase the risk of cardiovascular disease progression, more in female than in male. (Arfvidsson, Wennmalm, Gelin, et al. 1992; Colwell, 1997; Ogawa, Nakayama, Morimoto, et al. 2008). The mechanism of elevation incidence in cardiovascular disease remains not entirely understood. In fact, having diabetes mellitus doubles a woman's risk of developing cardiovascular disease (Larsen, & Lasen, 1966; Hayden, Pignone, & Phillips, 2002). Patients with a history of peripheral artery disease have the same relative risk of cardiovascular death as patients with coronary or cerebrovascular disease (Thomas, Elliott, Naughton, 2009; Larose, Sigal, Khandwala, et al. 2012).

Peripheral artery disease is a result of atherosclerotic disease progression, and it is not surprising that patients with peripheral artery disease are higher exposed to myocardial infarction, stroke, and all-cause mortality risk (Snowling, Hopkins, 2006; Gordon, Benson, Bird, et al. 2009; Colberg, Sigal, Fernhall, et al. 2010). The evidence proved that lifestyle modification with dietary modification and smoking cessation, combined with regular physical activity has an independent cardio-protective effect which may reduce overall cardiovascular risk. Using acetylsalicylic acid therapy (75-162 mg/d per day) in men age 45-79 years and women age 55-79 years, with or without diabetes, is a primary prevention strategy in patients having increased cardiovascular risk, including those who have additional risk factors (positive family history of cardiovascular disease, hypertension, smoking, dyslipidemia, or albuminuria) (Cai, Qiu, Ju, & Sun, 2014). The main mechanism of acetylsalicylic acid (ASA) is to block thromboxane synthesis by acetylating platelet cyclooxygenase. This therapy has been used as a primary and secondary strategy to prevent cardiovascular problems in non-diabetic and diabetic patients. Multiple studies and large-scale collaborative trials in diabetic and non-diabetic patients, both male and female, confirmed that low-dose Acetylsalicylic acid (ASA) therapy should be prescribed as a secondary prevention strategy (Sigal, Kenny, Boulé, et al. 2007; Brun, Bordenave, Mercier, et al. 2008; Karstoft, Winding, Knudsen, et al. 2013). The recognition that physical activity with life style modification and low-dose of acetylsalicylic acid (ASA) 150 mg/ per day can increase the symptoms reduction in stadium IIa of peripheral artery disease and reduce progression of cardiovascular problems, caused the therapy became the most ideal

treatment in diabetic and non-diabetic patients, age over 55, with mild or moderate claudication symptoms (AACPR, 2004; Ogawa, Nakayama, Morimoto, et al. 2008). This strategy is a trend toward increasing risk reductions in diabetic and non-diabetic patients, allowing significant increases in walking distance and improving quality of life in general. Physical activity magnified blood flow through this collateral circuitry in animal models of peripheral artery disease. Improvements in collateral-dependent blood flow to hind limb muscles that occur with regular physical activity come to remolding and enlargement of collateral vessels and alternative blood routes. The capability of physical activity combined with irregular acetylsalicylic acid (ASA) therapy and life style modification to alter the reactivity of collateral vessels has remained relatively unexplored (Jennings, Alberga, Sigal, et al. 2009; Plotnikoff, Eves, Jung, et al. 2010).

The aim of the study was to estimate the increasing capability of mild claudication distance in Fontaine's stage IIa of peripheral artery disease by influence of irregular acetylsalicylic acid (ASA) therapy and life style modification with regular physical activity in diabetic patients, without diabetic neuropathy and non-diabetic patients, after one year study at the Clinic of vascular surgery Clinical Center University of Sarajevo.



Picture 1: Digital subtraction angiography (DSA) medical report shows multiple femoro-popliteal lesions significant hemodynamic obstructions of femoral and popliteal artery lumen over 50% (Clinic for Vascular Surgery Clinical Center of University of Sarajevo, BIH)

2. Method

The research was executed as a case retrospective study, which included the period of validity of one year; during it, the group of patients in stadium IIa of peripheral artery disease with or without diabetes mellitus was observed. This study was conducted at the Clinic of vascular surgery, Clinical Center University of Sarajevo and included 60 patients of both genders, age over 55, with verified Femoro-Popliteal Stenosis over 50%, with or without diabetes mellitus, being in Fontaine's stage IIa of peripheral artery disease, with manifestations of mild claudication symptoms, who met the criteria for being included in the study. Interval training program was composed as described: walking of 30-60 minutes, with repetitions of 100-200m, middle intensity, fast walking with a recovery period following each repetition, also with self-control heart frequency 120-155 beats/min at max. intensity of 60 to 70% of heart rate, during at least one year, 4-6 times a week. This study was conducted at the Clinic for vascular surgery, Centre of Sarajevo University and included 60 patients, male and female, with diabetes mellitus and without diabetes mellitus, which met the criteria for including in the study. Patients were divided into two groups; the first group consisted of 30 diabetic patients with non-insulin resist. The first group consisted of 30 patients, who have diabetes mellitus; impellers group consists of 30 patients, clinically confirmed not to have diabetes mellitus. During period of one year research in non-diabetic and diabetic patients, progress of underlying disease was not confirmed; diabetic neuropathy and the presence of absence of lower limb and foot sensibility also, were not clinically confirmed during the study period. During one year training program procedure all diabetic patients were required to contact vascular surgeon and his medical team if health conditions become progressively worse (ulcus throphoneuroticum/traumaticum, other signs of foot ulceration, cold foot ischemia in progress, absence of sensibility, cancer, heart-attack, angina pectoralis, insulin therapy modification, etc.). Diabetic patients should also consume more complex carbohydrates, oligo and polysaccharides in form of cereals, combined with glass of orange juice and certain quantity of still water, at least one hour before working out. Main influence and attention of study is dedicated to diabetic patients because of complications of underlying disease.

All the patients, in spite of basic recommendation concerning combined treatment benefits (invasive or minimal-invasive reconstruction of PTA/stent/bypass) denied and refuse surgical treatment and have chosen conservative method of curing. The antiplatelet therapy in patients (diabetic and non-diabetic) was also changed (150 mg of acetylsalicylic acid (ASA) per day/75 mg each 12 hours during one year,

compared with 100 mg of acetylsalicylic acid (ASA) a day, before research started. At the research beginning, all the patients were also physically examined by a medical team, led by vascular surgeon and his medical team, as well as at the end of the research. The study was approved by an institutional review board and all patients gave their written consent.

3. Results

Table 1: Gender distribution in diabetic and non-diabetic patients

			Group		Total
			Patients who suffer from diabetes mellitus	**Patients who didn't suffer from diabetes mellitus**	**Total**
Gender	Male	N	23	25	48
		%	76,7	83,3	80,0
	Female	N	7	5	12
		%	23,3	16,7	20,0
Total		N	30	30	60
		%	50,0	50,0	100,0

Table 2: The period of Acetylsalicylic acid (ASA) therapy in diabetic and non-diabetic patients age over 55 years

Dose of Acetylsalicylic acid (ASA) 150 mg/ per day		Group		Total
		Patients who suffer from diabetes mellitus	**Patients who didn't suffer from diabetes mellitus**	**Total**
1 year of using Acetylsalicylic acid (ASA) therapy	N	2	13	15
	%	6,7	43,3	25,0
6 mounths of using Acetylsalicylic acid (ASA) therapy	N	3	5	8
	%	10,0	16,7	13,3
2 years of using Acetylsalicylic acid (ASA) therapy	N	4	3	7
	%	13,3	10,0	11,7
3 years of using Acetylsalicylic acid (ASA) therapy	N	5	5	10
	%	16,7	16,7	16,7
4 years of using Acetylsalicylic acid (ASA) therapy	N	16	4	20
	%	53,3	13,3	33,3
Total	N	30	30	60
	%	50,0	50,0	100,0

Table 3: Estimation of claudication distance in diabetic and non-diabetic patients age over 55 years

Claudications distance with mild claudication symptoms in meters				
Claudications distance in meters		**Group**		**Total**
		Patients who suffer from diabetes mellitus	**Patients who didn't suffer from diabetes mellitus**	
400m	N	3	2	5
	%	10,0	6,7	8,3
500m	N	4	3	7
	%	13,3	10,0	11,7
600m	N	9	4	13
	%	30,0	13,3	21,7
700m	N	7	10	17
	%	23,3	33,3	28,3
800m	N	5	5	10
	%	16,7	16,7	16,7
900m	N	2	5	7
	%	6,7	16,7	11,7
1000m	N	0	1	1
	%	,0	3,3	1,7
Total	N	30	30	60
	%	50,0	50,0	100,0

Table 4: Presence of a claudication distance with non-clinical symptoms of Peripheral artery disease after one year research

		Group		**Total**
		Patients who didn't suffer from diabetes mellitus	**Patients who suffer from diabetes mellitus**	
Yes	N	25	12	38
	%	83,3	40,0	46,7
No	N	5	18	23
	%	16,7	60,0	53,3
Total	N	30	30	60
	%	50,0	50,0	100,0

Table 5: Increasing of claudication distance in diabetic and non-diabetic patients over 500m after one year research

		Group		Total
		Patients who did not suffer from diabetes mellitus	Patients who suffer from diabetes mellitus	
Yes	N	30	30	60
	%	100	100	100
No	N	0	0	0
	%	0	0	0
Total	N	30	30	60
	%	50,0	50,0	100,0

In our analysis we documented statistically significant difference in higher incidence between patients using acetylsalicylic acid, compared with period before using ASA; in 16 (53%) patients with diabetes mellitus in over 4 years period ($p<0.05$). The 13 non-diabetic patient (43,3%) were statistically treated with acetylsalicylic acid in one year period ($p<0.05$). Separate analysis was done in males and females, patients with or without diabetes mellitus. Comparison of main values by gender shows that there were more males represented in the group of diabetics (76,7%) and non-diabetics, (83,3%) within no statistically significant differences within those groups ($p>0.05$). In this research we also documented the evaluation of claudication distance in diabetic patients and non-diabetic patients, which leads to conclusion that 10 (33,3%) of diabetic patients have reported claudication distance over 700m, compared to 9 (30%) non-diabetic patient, which have reported claudication distance over 600m, with no statistically significant differences in the groups ($p>0.05$). Only 3 (3,3%) non-diabetic patients documented the claudication distance over 1000m ($p>0.05$). The lower claudications distance of 400m was reported in 2 diabetic patients (6,7%) and 3 non-diabetic patients (10%).

4. Discussion

The study was based on data from history of disease and questionnaire carried out in all patients. During this study we have concluded that patients age over 55, who suffered from diabetes mellitus as a main unpredictable risk factor (Fontaine's stage IIa) of peripheral artery disease also suffer from collateral circulation deficiency, as a result of significant arterial destruction. Diabetes mellitus as accompanied disease of peripheral artery disease may increase disorders, which affects, either directly or

indirectly the functions of the arterial and collateral arterial system. The differences in effect of acetylsalicylic acid therapy between diabetic patient's age over 55 without diabetic neuropathy and non-diabetic patient's age over 55 were detected. As a summary review we have verified with continuous monitoring the statistical significant presence of a claudication distance with non-clinical or subjective symptoms of peripheral artery disease after one year of study in our data analysis in (83,3%) or 25 non-diabetic patients ($p<0,05$). We have proved the importance of connection between diabetes and a progression of peripheral artery disease, so that those patients should be more adequately treated by remolding the actual therapy. Enlargement of the collateral vessels (alternative blood routes) in diabetic patients is a main problem of underlying disease. Available evidence shows, however, that appropriate antiplatelet therapy in form of acetylsalicylic acid, physical activity and life style modification tends to increase the claudication distance and with mild symptomatic pain in Fontaine's stage IIa of peripheral artery disease statistically only in case of non-diabetic patients. Strategies for the body is to adapt and modified alternative blood circulation system by development of smaller peripheral arteries that will provide many pathways of blood flow around the ischemic area. This indicates that patients with mild claudicaton symptoms in Fontaine's stage IIa, in order to follow this strategic concept should be able to increase the claudication distance and return symptomatic stage of peripheral artery disease in asymptomatic stage of peripheral artery disease.

Patients with diabetes have potentially high level of arterial system destruction, increasing directly the cardiovascular risk and accelerating rapidly the development of peripheral artery disease. Adequate, regular, and timely therapy may prevent or delay these diabetic complications. Patient should be aware of the important relationship between diabetes and atherosclerosis and be prepared to be appropriately medically treated to reduce disability and avoid arterial diabetic complications. In study by Edward P Weiss and co. „*Effects of matched weight loss from calorie restriction, exercise, or both on cardiovascular disease risk factors*": Reductions in body weight have substantial beneficial effects on cardiovascular (CVD) risk factors, so that with certainty we have proved that Interval Training Exercise Program and Life Style Modification (with sugar intake restriction, and reducing animal fat nutrition source) is vascular-protective modifying the alternative blood circulation with increasing the pain tolerance and returning to asymptomatic stage of peripheral artery disease (Weiss, Albert, Reeds et al. 2016). Also the study by Byrne, Caulfield., & De Vito, 2015 "*Effects of Self-directed Exercise Programmes on Individuals with Type 2 Diabetes Mellitus*" indicated that self-directed exercise was found to be beneficial for diabetic individuals for improving

glycosylated hemoglobin, physical characteristics, cardiorespiratory fitness, functional measures and other metabolic outcomes. Physical activity with life style modification and appropriate antiplatelet therapy in form of acetylsalicylic acid 150mg/d (75 mg every 12 hours) should be implemented in diabetic and non-diabetic patients and unless it is contraindicated by risk of gastrointestinal bleeding (gastric mucosal injury and gastrointestinal hemorrhage) or using alternative solution (clopidogrel 75mg/d). The role of physical exercise and training in the management of diabetes mellitus is more than recommended. This strategy would be helpful in the management of patients which were also connected with cardiovascular risk, depending on use of other effective techniques for cardiovascular risk reduction, including statins if necessary, blood pressure control, and smoking cessation. These combined therapies could be good alternative, in order to avoid unnecessary surgical treatment. The diabetic patients have to take special attention to their life style, having more discipline then non-diabetic patients. Working out is very important for establishment of collateral alternative blood vessel system, independently of taking aspirin. Of course, continuous taking of ASA would, maybe, has better effect on clinic benefits for atherosclerosis in diabetic and non-diabetic patients, as well as long-lasting taking; further research is necessary for confirming this statement. Atherosclerosis as a form of stadium IIa of peripheral artery disease is significantly reduced by increasing the claudication distance over 500m after one year of study in diabetic and non-diabetic patients, using this combined therapy. Strategies for collateral re-vascularization must have been taken into consideration as well as in the diabetic patients and non-diabetic patients.

5. Conclusion

Interval exercise training strategy and appropriate antiplatelet therapy should been incorporated into current guidelines for the management of peripheral artery disease in Fontaine's Stage II in patients who denied and refuse surgical treatment because of its potential health benefits, in order to avoid certain or potential invasive or minimal invasive surgical interventions.

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